

# Leukaemia Section

## Short Communication

### t(4;11)(q23;p15) NUP98/RAP1GDS1

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Published in Atlas Database: January 2016

Online updated version : <http://AtlasGeneticsOncology.org/Anomalies/t0411q23p15ID1191.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/66940/01-2016-t0411q23p15ID1191.pdf>

DOI: 10.4267/2042/66940

This article is an update of :

Viguié F. t(4;11)(q21;p15). *Atlas Genet Cytogenet Oncol Haematol* 2002;6(4)

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## Abstract

Review on t(4;11)(q23;p15) NUP98/RAP1GDS1, with data on clinics.

## Identity

The t(4;11)(q23;q15) is a rare but recurrent translocation strongly associated with T-cell acute lymphoblastic leukemia (T-ALL). This translocation results in a novel gene fusion of NUP98/11p15 and RAP1GDS1/4q23 genes [Figure 1]. Therefore, t(4;11)(q23;p15) is NOT a variant of the t(4;11)(q21;q23) involving the AFF1 and KMT2A (MLL) genes, as previously presumed.

## Clinics and pathology

### Disease

The t(4;11)(q23;p15) is mostly described in an early precursor T-cell ALL of thymic origin. Only two cases with acute myeloid leukemia (AML) were reported with this translocation; the t(4;11)(q23;p15) with NUP98/RAP1GDS1 fusion expression was identified in a patient with AML-M0 at time of diagnosis. Whereas the second case was with AML-M4, in which the t(4;11)(q23;p15) was detected at relapse with a normal karyotype at diagnosis.

### Phenotype/cell stem origin

Bone marrows are hypercellular with a massive infiltration (~90%) with lymphoblasts of L1 or L2 morphology. Whereas different markers are tested

for each case, leukemic cells are generally positive for CD3, CD5, CD7, CD10, TdT, and thymic associated marker CD1a, negative or partially expressing CD2, CD4, and CD8. One or more myeloid markers CD11b, CD13, and/or CD33 are co-expressed in some patients. This suggests that NUP98/RAP1GDS1 fusion occurs in subset of T-ALL originated from an early progenitor with a potential to express mature T-cell antigens as well as myeloid markers.

### Epidemiology

Patient's ages are ranged from 6 to 60 years, with a predominance of younger individuals (60% <= 25 years) as is classic for T-cell ALL. None of the patients with this translocation was an infant. The t(4;11)(q23;p15) seems to be extremely rare and its exact incidence in leukemia is difficult to establish. In large studies, t(4;11) was identified in approximately 2% adult and in 0.3% children with T-ALL while other studies have failed to detect a single case.

### Clinics

Most patients present with a high WBC counts with a high proportion of blasts, generalized lymphadenopathy and mediastinal mass but hepatosplenomegaly is less frequent.

### Prognosis

The risk associated with t(4;11)(q23;p15.4) is not well determined due to low number of cases although most patients with this translocation had a short survival.

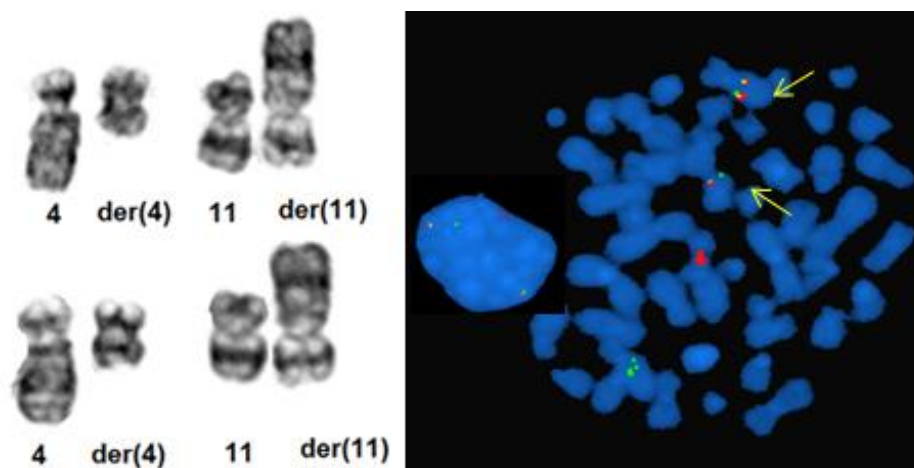


Figure 1; Left; Partial karyotype showing t(4;11)(q23;p15), Right; FISH showing a double fusion pattern of NUP98-RAP1GDS1 genes.

## Cytogenetics

Karyotype is relatively simple with t(4;11)(q23;p15) a sole abnormality in 5/13 cases (Table 1).

### Cytogenetics morphological

See Table 1.

### Additional anomalies

One or two additional abnormalities were seen in 8/13 cases including del(12p) in two cases; del(5q), del(9p), del(13q), or trisomy 8 in a single case each.

### Variants

t(1;4;11)(p32;q21;p15) was reported in one case.

Patient	Leukemia	Age/ Sex	WBC 10 <sup>9</sup> /L	Karyotype	Fusion Genes	Outcome	References
1	T-ALL L1	21/M	423	46,XY,t(4;11)(q21;p15),+2mar	NUP98/RAP1GDS1	Relapsed after 2 matched BMT; died 43 M	Hussey et al., 1999
2	T-ALL L1	25/F	1.8	46,XX,t(4;11)(q21;p14-15),del(12)(p13),+del(13)(q12q14)	NUP98/RAP1GDS1	Failure of induction; Died 1M later	Hussey et al., 1999
3	T-ALL L2	49/M	169	46,XY,t(4;11)(q21;p15),del(5)(q13q31)	NUP98/RAP1GDS1	BM remission, early relapse, died 14 M	Hussey et al., 1999
4	T-ALL L2	16/F	34	47,XX,t(4;11)(q21;p15),+8	NUP98/RAP1GDS1	CR, followed by BMT; 7 m+	Mecucci et al., 2000
5	T-ALL L2	38F	35	47,XX,t(4;11)(q21;p15),+mar	NUP98/RAP1GDS1	CR, relapsed in 8 m; died after BMT	Mecucci et al. 2000
6	AML-M0	60/F	3.9	46-t(4;11)(q1?3;p15),?der(8)(p?)	NUP98/RAP1GDS1	CR; relapsed and died 8m after diagnosis	van Zutven et al, 2006
7	T-ALL	15/M	72.8	46,XY,t(4;11)(q23;p15),del(9)(p13)	NUP98/RAP1GDS1	CR obtained, survival 7M+	Present case, 2015

**Table 1:** Reported acute leukemia cases with t(4;11)(q21-q23;p15) and NUP98/RAP1GDS1 gene fusion.

## Genes involved and proteins

### ***RAP1GDS1 (RAP1, GTP-GDP dissociation stimulator 1)***

#### **Location**

4q23

#### **DNA/RNA**

RAP1, GTP-GDP dissociation stimulator 1 (RAP1GDS1) is a gene that encodes a protein that functions as a stimulatory GDP/GTP exchange protein with GTPase activity. Fusions, missense mutations, nonsense mutations, silent mutations, frameshift deletions, and in-frame deletions are observed in cancers such as endometrial cancer, intestinal cancer, and skin cancer.

#### **Protein**

RAP1GDS1 encodes a 558-amino acid protein with a molecular mass of 61.1 kD. The product of the RAP1GDS1 gene, usually referred to as smgGDS, has guanine nucleotide exchange factor activity. It stimulates the conversion of inactive GDP-bound from small GTPases to the active GTP-bound form. It has been speculated that smgGDS might also play a role in nucleocytoplasmic transport, as smgGDS is composed of multiple armadillo repeats that are thought to mediate protein-protein interactions. SmgGDS has been described as a "master regulator" of small GTPases, such as RHOA, RAC1, RAP1A, RAP1B, and KRAS. SmgGDS controls the activities of these GTPases through several mechanisms, most notably by controlling their prenylation and trafficking to cell membranes. The ability of smgGDS to regulate the cell cycle in multiple cancer cell lines with different mutational profiles indicates the importance of this protein as a key regulator of malignancy. SmgGDS is overexpressed in multiple types of cancer, including non-small cell lung carcinoma, prostate cancer, pancreatic cancer and breast cancer, making SmgGDS an attractive target for cancer therapeutics.

### ***NUP98 (nucleoporin 98 kDa)***

#### **Location**

11p15.4

#### **DNA/RNA**

NUP98 is one of several genes located in the imprinted gene domain of chromosome 11p15. Combined haploinsufficiency of NUP98 and RAE1 has been shown to result in premature separation of sister chromatids, leading to severe aneuploidy. NUP98 plays roles in gene expression, mitotic spindle formation, and cell cycle progression. NUP98 gene is fused to a large number of "partner genes" caused primarily by balanced translocations

and inversions which are associated with a wide variety of hematological malignancies including AML and MDS (de novo and therapy related), CML-blast crisis, and pre T-ALL. To date, no NUP98 fusion gene has been described in B-cell malignancies. At least 30 different partner genes are reported to fuse with NUP98; 50% of which are homeobox genes. Approximately 10% of patients with NUP98 fusions have T-ALL; most commonly, these malignancies are associated with NUP98-RAP1GDS1 gene fusions. This suggests that different partner genes are associated with different leukemia, although such associations are rarely exclusive. Although NUP98 breakpoints in these translocations are variable located between introns 9 to 14, a chimeric transcript consisting of the 5' portion of NUP98 fused in-frame to the 3' portion of the partner genes is generated in all.

#### **Protein**

NUP98 gene encodes two alternatively spliced mRNA variants: NUP98 and NUP98-NUP96 that are cleaved to produce two distinct nucleoporins, NUP98 and NUP96. The NUP98 is a 98 kDa protein component of the nuclear pore complex (NPC) family which is involved in the trafficking of RNA and protein between the nucleus and cytoplasm. The NUP98 protein contains two partially characterized functional domains: a GLFG repeat region, which serves as a nuclear transport receptor docking surface, and a GLEBS domain, which mediates the interaction with the RAE1 mRNA nuclear export factor. Both domains are located within the N-terminal portion of NUP98. The chimeric NUP98 protein that results from translocations always retains the intact N-terminal GLFG repeats of NUP98 and the C-terminal domain of the partner protein. NUP96 is a scaffold component of the NPC.

## Result of the chromosomal anomaly

### ***Hybrid gene***

Of the 13 cases reported in the literature with t(4;11)(q23;q15); seven cases showed NUP98/RAP1GDS1 gene fusion while the status of these genes were not tested in the remaining five cases (Table 1).

### ***Fusion protein***

#### **Description**

T(4;11) generates two reciprocal chimeric products; chimeric 5'NUP98 -3'RAP1GDS1 transcript produces a novel protein composed of the N-terminal portion of the NUP98 protein and the entire smgGDS which is anticipated to promote leukemogenesis. However, the reciprocal 5'

RAP1GDS1-3'NUP98 transcript is often but not always expressed.

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*This article should be referenced as such:*

Anwar N Mohamed. t(4;11)(q23;p15) NUP98/RAP1GDS1. *Atlas Genet Cytogenet Oncol Haematol*. 2016; 20(11):579-582.

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